Lecture 2+3 - Cell Wall Inhibitors:

Some antimicrobial drugs selectively interfere with the synthesis of bacteria cell wall. Unique to bacteria, this structure is not found in mammalian cells. These agents require actively proliferating microorganism; they have little or no effect on bacteria that are not growing. The most important members of the group are the β-lactam antibiotics

ß-lactam compounds: The name comes from effective part which is ß-lactam ring

Mechanism of action of ß-lactam compounds:

All ß-lactam compouds have the same bactericidal mechanism of action. They inhibit the synthesis of cell wall in bacteria. This occur by binding of the antibiotic with certain enzymes called penicillin binding proteins (PBP_s) that catalyze the final stage in cell wall synthesis. Cell lysis can then occur, either through osmotic pressure or through the activation of autolysins. The success of a penicillin antibiotic in causing cell death is related to the antibiotics size, charge and hydrophobicity. Penicillins are only effective against rapidly growing organisms that synthesize a peptidoglycan cell wall. Consequently, they are inactive against organism devoid of this structure, such as mycobacteria, fungi, and viruses.

Mechanism of resistance to ß-lactam compounds:

Bacterial resistance to ß-lactam may occur by one of the following mechanisms or a combination of these:

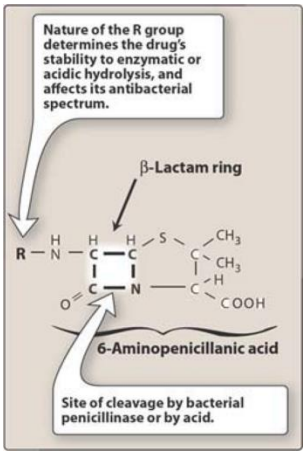
1) Inactivation of ß-lactam ring by certain bacteria possess ß-lactamase or penicillinase enzyme that inactivate the antibiotic.
2) Alteration or modification of bacterial PBP_s.
3) Reduce affinity of antibiotic to bind PBP_s.

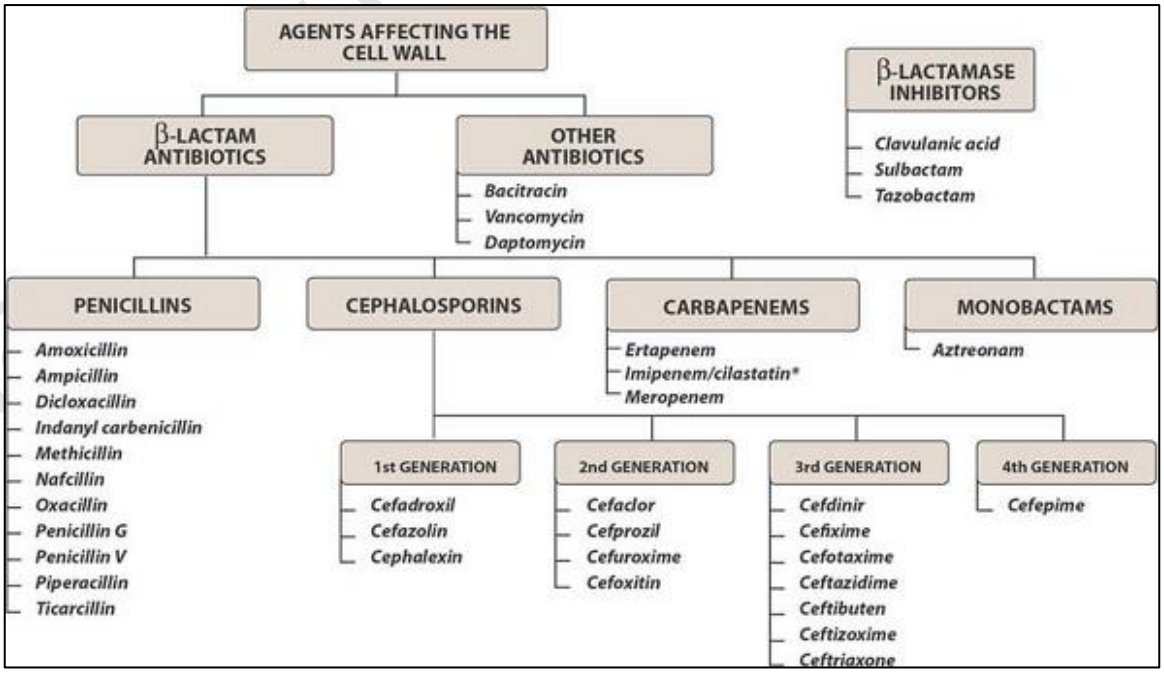
The ß-lactam compounds include:

A. Penicillins:

They are the most widely effective antibiotic and the low toxic effect. The basic structure of this compound is the 6-aminopenicillianic acid, members of this group in the R-side chain. The nature of this side chain affects the antimicrobial spectrum, the stability to stomach acids and susceptibility to bacterial degredative enzymes which degrade ß-lactam ring.

The structural integrity of the 6-aminopenicillianic acid is essential for biological activity of these compounds. If the ß-lactam ring is enzymatically cleaved by bacterial ß-lactamase, the resulting product which is called penicilloic acid will lack the antibacterial activity.





Penicillins are bactericidal antibiotic and are divided according to their spectrum of activity to:

1) Narrow spectrum natural penicillins

The antibacterial activity of narrow spectrum penicillins include mainly G+ve bacteria as staphylococci, most strains of streptococci, meningeococci and anaerobes and Gve- bacteria as Neisseria, Pasturella.

a) Benzylpenicillin (penicillin G)

- It is destroyed by gastric acidity so it is not suitable for oral uses; it is given by injection, sensitive to ß-lactamase producing by bacteria.
- Short half-life less than 2hrs, penetrates in most tissues.
- Elimination of pencillin G is mainly thorough kidneys by active tubular secretion. This type of elimination can be inhibited by administration of probencid that result in longer duration of action.

Typical therapeutic application of penicillin G in fig below

b) Phenoxymethlpenicillin (penicillin V)

Is given orally because of good absorption but food decrease its bioavailability. Pencillin V achieves lower serum concentration than penicillin G when high serum concentration is required.

c) Procaine penicillin

This combination results in longer duration of action (up 24hrs). This preparation is less painful at site of injection.

d) Benzathine penicillin

Its longer-acting penicillin that persist in blood for 4 weeks but in low concentration. It is useful in prophylaxis of rheumatic fever.

The clinical uses of natural penicillins include

staphylococcal infection; streptococcal pharyngitis and endocarditis; meningitis; pneumonia; bronchitis; anthrax; otitis media; sinusitis; clostridium infections and syphilis.

2) Antistaphylococcal penicillins (β-lactamase resistance drugs)

- Certain bacteria tend to produce β-lactamase which opens the β-lactam ring common to all penicillins and thus terminate the antibacterial action.
- The antistaphylcoccal penicillins drugs resist the action of β-lactamase by presence of an acyl side chains that protect the β-lactam by preventing the enzyme getting access to it.
- Drugs of this group:

➢ **Cloxacillin:** resists degredation by gastric acid and is absorbed from the gut but food interferes with absorption.

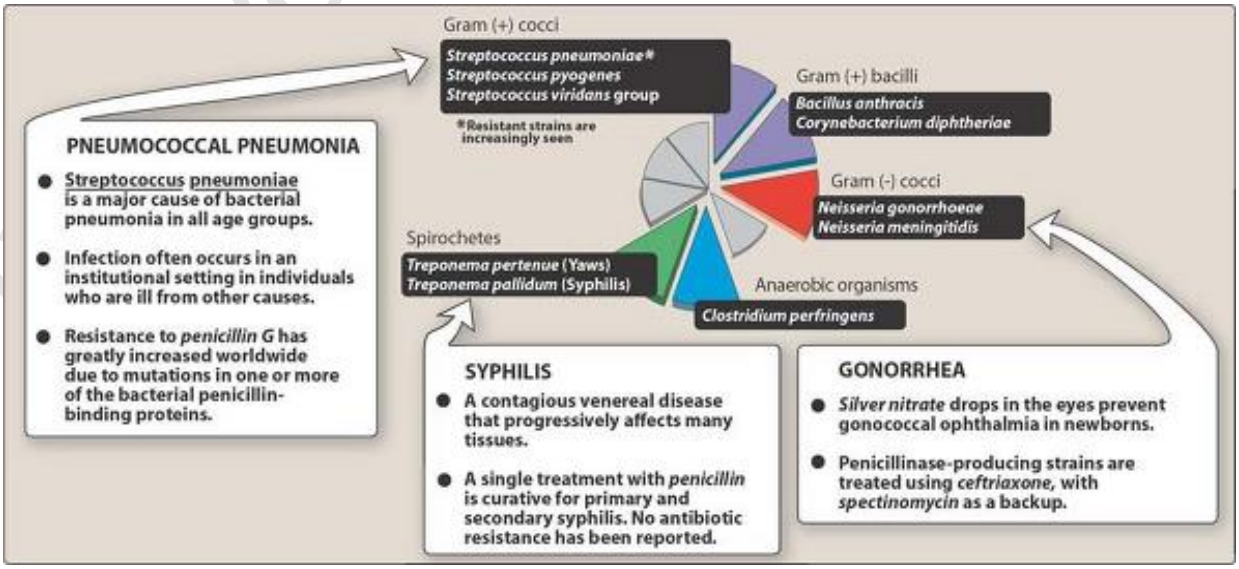
➢ **Flucloxacillin:** is more fully absorbed and so gives higher blood conc. than dose cloxacillin.

➢ **Methicillin:** is rarely used because of causing interstitial nepheritis. Methicillin -resistance strains of staphylococcus aureus (MRSA), these m.o also resistance to cloxacillin and flucloxacillin. These types of infection are usually susceptible to vancomycin and rarely to ciprofloxacin or rifampcin.

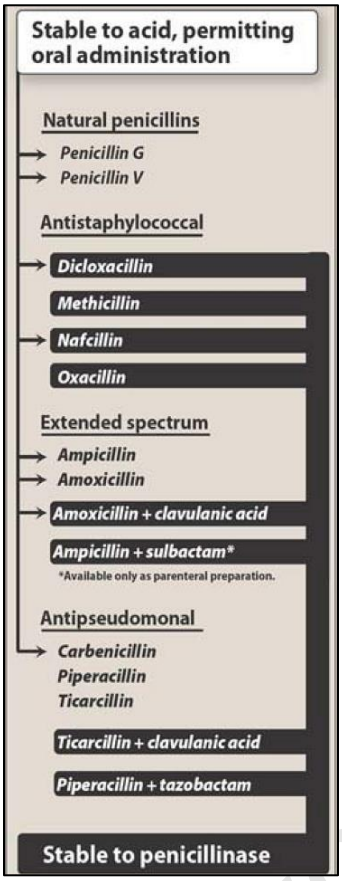
3) Extended spectrum penicillins

Have an antibacterial spectrum similar to that of penicillin G, but are more effective against G-ve bacilli. as E.coli, H.influenza, proteus mirabills and salmonella typhi. They have less activity than benzylpenicillin against streptococci. They are β-lactamase sensitive, these drugs are:

a) **Ampicillin:** it is acid stable, given orally but food interferes with its absorption, also it can be given I.M or I.V. Ampicillin attains high concentration in CSF. Ampicillin is sensitive to penicillinase- enzyme thus it is combined with sulbactam to resist inactivation by bacterial enzymes.



b) **Amoxicillin:** it is an analogue of ampicillin that is better absorbed from the gut and food does not interfere with its absorption. It does not achieve adequate concentration in the CSF to be useful in meningitis. Amoxicillin is sensitive to β-lactamase enzyme thus it is combined with clavulanic acid under the trade name Amoxiclave to resist bacterial degradation. Diarrhea appears to be less frequent with amoxicillin than ampicillin.



Aminopenicillins: as Ampicillin and Amoxicillin.

4) Antipseudomonal penicillins drugs: are of 2 types

a) **Carboxypenicillins:** They have some antimicrobial activity as penicillin, but additional effect in destroying pseudomonas aerogenosa and proteus Vulgaris. Include **Carbinecillin** and **Ticarcillin**. These drugs are inactivated by β-lactamase so it is combined with clavulanic acid to resist bacterial inactivation.

b) **Uridopenicillins:** This group include **piperacillin** and **azlocillin**. Piperacillin is slightly greater efficacy as the azlocillin but more affective against G-ve microorganism. Usually given combined with β-lactamase inhibitor (Tazobactam).

Adverse effects of penicillins

- **Allergic reaction** as skin rashes, bronchospasm and may cause anaphylactic shock.
- **Diarrhea:** this due to disruption of the normal flora in the intestine.
- **Nephritis:** all penicillins, but particularly methicillin.
- **Neurotoxicity:** the penicillins are irritant to neuronal tissue may induce seizures if injected intrathecally or if very high blood level are reached.
- **Platelet dysfunction:** involves decreased agglutination, is observed with antipseudomonal penicillins and with some extent with penicillin G.
- **Cation toxicity:** Usually penicillins administered as Na or K salts. Toxicities may be caused by the large quantities of sodium or potassium that accompany the penicillin. Sodium excess may result in hypokalemia. This can be avoided by using the most potent antibiotic.

Pharmacokinetics of penicillin:

- **Administration:** the route of administration of a β-lactam antibiotic is determined by stability of the drug to gastric acid and by the severity of the infection. Ticarcillin, carbinicillin, piperacillin, and the combinations of ampicillin with sulbactam, ticarcillin with clavulinic acid, and pieracillin with tazobactam must be administered intravenously or intramuscularly. Penicillin V, amoxicillin, amoxicillin combined with clavulanic acid and indanyl carbenicillin (for treatment of urinary tract infections) are only available as oral preparations. Others are effective by the oral, IV, IM routes.

- **Absorption:** most of the penicillin are incompletely absorbed after oral administration, and they reach the intestine in sufficient amounts to affect the composition of the intestinal flora. However amoxicillin is almost completely absorbed.
  Consequently, it is not appropriate therapy for the treatment of shigella- or salmonella-derived enteritis, because therapeutically effective levels do not reach the organisms in the intestinal crypts. Absorption of all penicillinase-resistant penicillins is decreased by food in the stomach. Therefore, they must be administered thirty to sixty minutes before meals or two to three hours postprandially. Other penicillins are less affected by food.

- **Distribution:** Distribution of the β-lactam antibiotics throughout the body is good. All the penicillins cross the placental barrier, but none has been shown to be teratogenic.

However, penetration into certain sites, such as bone or cerebrospinal fluid (CSF), is insufficient for therapy unless these sites are inflamed. During the acute phase of infection, the inflamed meninges are more permeable to the penicillins, resulting in an increased ratio of the amount of drug in the central nervous system compared to the amount in the serum. Penicillin levels in the prostate are insufficient to be effective against infections.

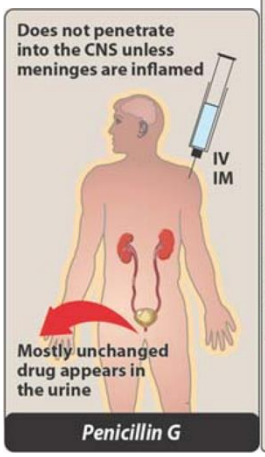


Figure 31.7 Administration and fate of *penicillin*.

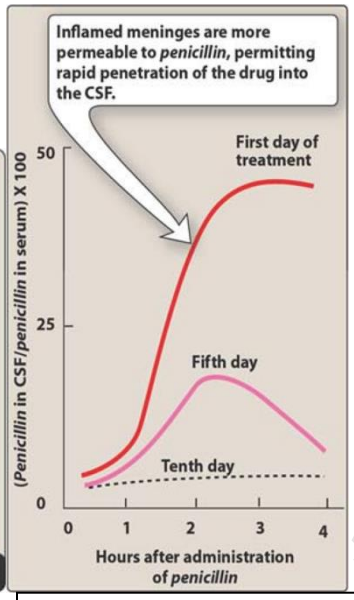
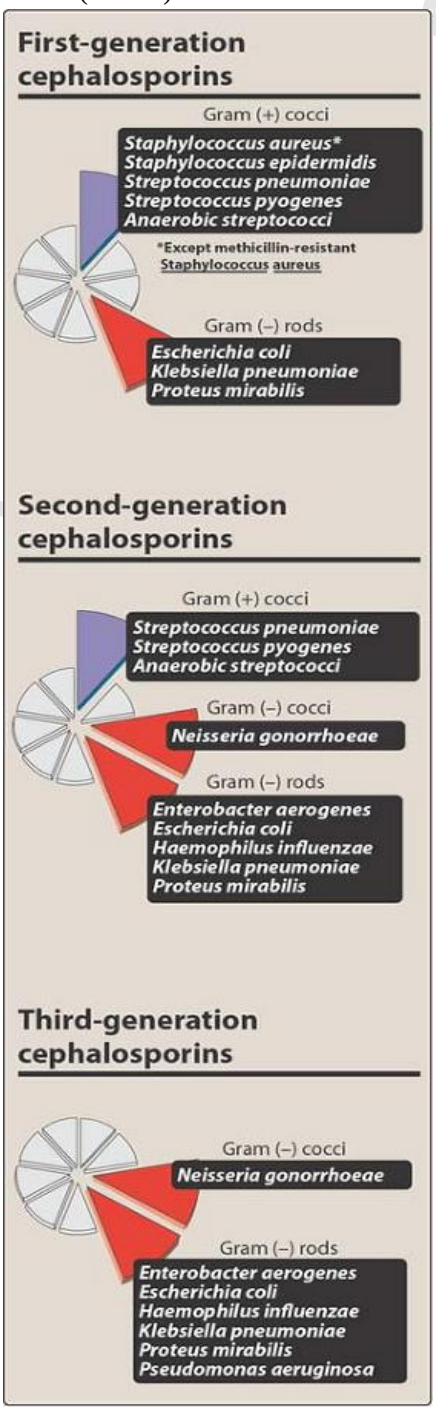


Figure 31.8 Enhanced penetration of *penicillin* into the cerebral spinal fluid (CSF) during inflammation.

- **Excretion:** The primary route of excretion is through the organic acid secretory system of the kidney as well as by glomerular filtration. Patients with impaired renal function must have dosage regimens adjusted. Thus the half-life of penicillin G can increase from a normal of 1 hour to 10 hours in individuals with renal failure. The penicillins are also excreted into breast milk and into saliva.

B. Cephalosporins

They are β-lactam antibiotics that are closely related to penicillin in chemical structure, mechanism of action, toxicity and function. Cephalosporins are classified into generation according to improvement in their spectrum of activity, potency and resistance to β-lactamase. They are ineffective against methicillin-resistant Staphylococcus aureus (MRSA).



1. First generation:

They are resistant to the staphylococcal penicillinase, the more useful drugs

Cephalexin: prototype of first generation oral cephalosporins. Oral administration four times daily.

Cefazolin:

It is a first-generation parenteral cephalosporin has a longer duration of action and a similar spectrum of action compared to other first-generation drugs. Good penetration into bone.

Other drugs: **cephadroxil, cephalothin** and **cephradine**.

Uses

Are useful in prophylaxis before surgery because most postoperative infection are caused by G+ve bacteria as staphylococci; treatment of skin, bone, wound, urinary tract and respiratory tract infection. First generation drugs are not used in meningitis because they do not enter CSF.

2. Second generation:

Active against m.o of first generation activity, but have extended G-ve effect. Less activity on G+ve than first generation.

Cefuroxime: it is prototype second-generation parenteral cephalosporin has a longer half-life than similar agents. It crosses the blood brain barrier but less activity than first generation.

Other drugs of this group

cefaclor, cephamandole, , ceforanide , cefonicid, cefoxitin ,cefotetan

Uses

Second-generation drugs are more resistant to β-lactamase inactivation with broad spectrum activity that include G+ve cocci, G-ve and anaerobes as bacteroides (including β-fragilis) and closteridum. They are used in sinusitis, otitis media, pneumonia, peritonitis and abscess like diabetic foot ulcer.

3. Third generation:

These agents have greatly inferior to first generation cephalosporins in regard to their activity G+ve cocci also they have enhanced activity against G-ve bacilli.

Ceftriaxone: longest half-life of any cephalosporin(6-8hrs) permit once a day dosing. High levels of drug can be achieved in blood and CSF. Effective against genital, anal and pharyngeal penicillin-resistant Neisseria gonorrhoeae. Drug excreted in bile and may be used in patients with renal insufficiency. Good penetration into bone.

Other drugs of this group:

Cefotaxime (good penetration into CSF), **cefixime** (oral dosing once daily), **ceftazidime** (active against pseudomoneas aeruginosa), **ceftizoxime** (has broad effect on G-ve and anaerobes particularly β.fragilis.

4. Fourth-generation:

Cefepime: Is the most clinically useful fourth generation agent. It has a wide antibacterial spectrum; it passes well to the CNS.

Uses

The infections of G-ve organisms especially those caused resistance to third generation drugs. Members of this generation are resistant to the action of bacterial β-lactamase.

Side effects

The cephalosporins produce a number of adverse effects, some of which are unique to particular members of the group.

1) **Hyper sensitivity reactions**: cephalosporins may produce several types of hypersensitivity reaction similar to penicillins. There is cross-allergy between cephalosporins and penicillins and about 5-10% of patients who have allergy to penicillins have allergy to cephalosporins too. Allergic reactions include urticaria and rashes.
2) **Local irritation**: cephalosporins produce sever pain after I.M inj so local anesthetic agent may be added. Cephalosporins may produce thrombophlebitis when given i.v.
3) A **disulfiram like effect** (hypotension, sweating & fainting). When cefamandole is ingested with alcohol or alcohol-containing medication, a disulfiram-like effect is seen because the cephalosporins block the second step in alcohol oxidation, which results in the accumulation of acetaldehyde.
4) **Bleeding:** bleeding can occur with cefamandole or cefotetan because of anti-vitamin k effects; administration of the vitamin corrects the problem.
5) Overgrowth of resistant strains of m.o. may produce organism resistant to all β-lactam antibiotics.
6) Mild and transient nausea, vomiting and diarrhea occur with the orally administered cephalosporins.

C. Monobactams:

Monobactams are resistant to β-lactamase, but they act only on G-ve bacteria (aerobic). It lacks activity against G+ve organism and anaerobes. The best drug of this group **Azetronam**. It is administered via IV or IM routes and it is mainly eliminated through kidney and can

accumulate in patients with renal failure. It is a safe alternative for treating patients allergic to penicillins and/or cephalosporins.

D. Carbapenems:

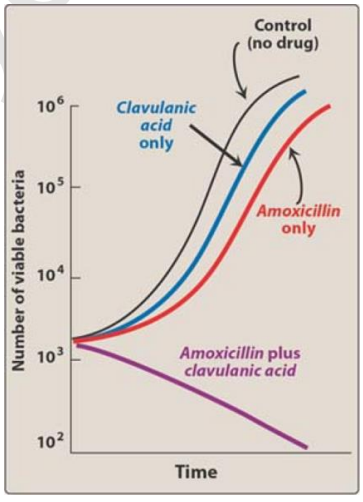
Are synthetic β-lactam antibiotics structurally similar to penicillins.

Imipenem: it is the most broad spectrum β-lactam antibiotics. It is **effective against** G-ve, G+ve aerobic bacteria and anaerobic m.o. imipenem resists hydrolysis by most β-lactamases. It is active against penicillinase-producing G+ve and G-ve organisms, anaerobes and pseudomonas aeruginosa, although other pseudomonas strains are resistant.

It is **administered by** i.v route and penetrates well into body tissues and fluids including CSF when the meninges are inflamed. It is excreted by glomerular filtration and undergoes cleavage by a **dehydropeptidase** found in the brush border of the proximal renal tubule to form an inactive metabolite that is potentially nephrotoxic. Compounding the imipenem with cilastatin, a dehydropeptidase inhibitor, protects the parent drug from cleavage and thus prevents the formation of a toxic metabolite. This allows the drug to be active in the treatment of urinary tract infections.

β-Lactamas inhibitors:

Hydrolysis of the β-lactam ring either by enzymatic cleavage via a β-Lactamase or by acid, destroys antimicrobial activity. β-Lactamase inhibitors such as: **Clavulanic acid, Sulbactam** and **Tazobactam** contain a β-lactam ring, but they do not have significant antibacterial activity. Instead, they bind to and inactivate β-Lactamases, their by protecting the antibiotics that are normally substrates for these enzymes. The β-Lactamase inhibitors are formulated with penicillin derivatives to protect the latter from enzymatic inactivation.



Growth of Escherichia coli in presence of amoxicillin, with and without of Clavulanic acid

Vancomycin

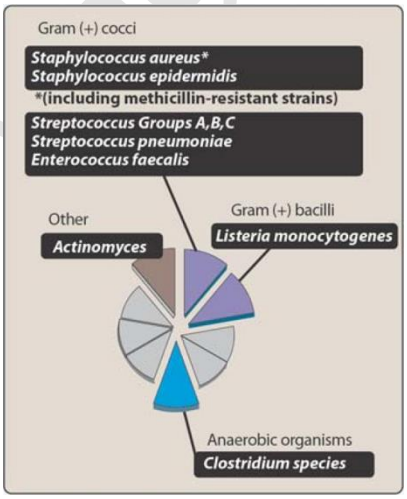
Its effectiveness against multiple drug resistance organisms such as methicillin-resistant staphylococci (MRSA) and enterococci. It is not a β-lactam drug.

Mechanism of action

Vancomycin inhibits synthesis of bacterial cell wall phospholipids as well as peptidoglycan polymerization by binding to the D-Ala-D-Ala side chain of the precursor pentapeptide. This prevents the transglycosylation step in peptidoglycan polymerization, thus weakening the cell wall and damaging the underlying cell.

Antibacterial spectrum: For infections caused by β-lactmase producing organisms and for patients with G+ve infection who have a serious allergy to penecillins.

Vancomycin acts synergistically with aminoglycosides and this combination can be used in the treatment of enterococcal endocardities.



Antimicrobial spectrum of vancomycin

Side effects: Ototoxicity which may result in deafness, fever and chills, maculopapular skin rashes in the face and chest (red man syndrome).